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ILLUMINA, INC.
9885 TOWNE CENTRE DRIVE
SAN DIEGO, CA 92121-1975

EXAMINER	
BERTAGNA, ANGELA MARIE	
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1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,634	GUNDERSON ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-15,17-19,21-26,28-34,36-51,53,54,64,66-72 and 78-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9-15,17-19,21-26,28-34,36-51,53,54,64,66-72 and 78-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/6/07; 3/7/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 7, 2007 has been entered. Claims 1, 3-7, 9-15, 17-19, 21-26, 28-34, 36-51, 53, 54, 64, 66-72, and 78-82 are currently pending and will be examined on the merits.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on March 6, 2007 is acknowledged. A signed copy is enclosed.

Applicant's submission of an Information Disclosure Statement on March 7, 2007 is also acknowledged. All of the references cited on the IDS were cited on the IDS filed on March 6, 2007 and considered as noted above. Accordingly, this duplicate IDS has not been considered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-7, 9-15, 17-19, 21-26, 28-34, 36-51, 53, 54, 64, 66-72, and 78-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-7, 9-15, 17-19, 21-26, 28-34, 36-51, 53, 54, 64, 66-72, and 78-82 are indefinite, because claims 1, 18, 37, and 64 recite hybridization to nucleic acid probes corresponding to typable loci. "Corresponding" is not an art-recognized term to describe the relationship between two nucleic acid sequences. It is unclear whether a corresponding nucleotide refers to a nucleotide that is at the same position or to a nucleotide that is a nearby position. It is also not clear if corresponding is intended to refer to a similar nucleotide at any position in a related (e.g. orthologous or paralogous) sequence. Since the term "corresponds" has not been clearly defined in the specification and is not an art-recognized term, one of ordinary skill in the art cannot determine the metes and bounds of the claimed subject matter.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 3, 6, 7, 9-12, 14, 15, 17-19, 22, 25, 26, 28-31, 33, 34, 36, 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dean et al. (US 6,617,137 B2; cited previously). This patent obtains benefit of US Application 09/977,868, filed October 15, 2001.

Regarding claim 1, Dean teaches a method of detecting typable loci of a genome, comprising:

(a) amplifying genomic DNA with a population of random primers, thereby providing an amplified representative population of genome fragments comprising said typable loci, wherein said population comprises a high complexity representation (column 37, lines 10-39)

(b) contacting the amplified representative population of genome fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed, wherein said probes are at most 125 nucleotides in length (column 16, lines 26-50 teaches address probes less than 125 nucleotides in length; column 18, lines 39-41 teach hybridization of amplification products to these surface-immobilized probes)

(c) detecting typable loci of said probe-fragment hybrids (column 16, lines 26-50 and column 18, lines 39-54).

Regarding claim 3, Dean teaches that the providing in step (a) comprises representationally amplifying a native genome (the amplification conducted in column 37, lines 10-39 is a representational amplification).

Regarding claim 6, Dean teaches the representational amplification is a single-step reaction yielding a high complexity representation (column 37, lines 10-39 teach a single-step procedure). As noted above, a "single step reaction" has been interpreted to mean a "closed tube" reaction, because according to the specification, the term "a single step reaction" only appears to differentiate between the pooling of multiple, separate amplifications and performing a single amplification reaction (paragraph 153). Also, in the Examples, only single amplification reactions comprising multiple different temperature steps were conducted to produce representationally amplified samples. Therefore, the disclosure of Dean meets the instant limitation.

Regarding claim 7, Dean teaches that at most 1×10^6 copies of said native genome are used as a template for amplification (column 39, lines 31-33, where 9 copies were used).

Regarding claim 9, Dean teaches that the substrate is a particle, a bead, a surface, a slide or a microchip (column 18, lines 23-38).

Regarding claim 10, Dean teaches that at least 100 typable loci are simultaneously detected (column 19, lines 51-52 teaches detection of 256 targets).

Regarding claim 11, Dean teaches that the genome is a human genome (column 37, lines 10-12).

Regarding claim 12, Dean teaches that step (b) of claim 1 comprises contacting the genome fragments with a multiplexed array of nucleic acid probes (column 18, lines 39-41).

Regarding claim 14, Dean teaches that the probes are nucleic acid probes that are at least 20 nucleotides in length (column 16, lines 26-50 teaches that the address probes described in column 18, lines 39-41 are less than 125 nucleotides in length, specifically 15-20 nucleotides in length).

Regarding claim 15, Dean teaches producing a report identifying said typable loci that are detected (column 17, lines 25-28).

Regarding claim 17, Dean teaches that step (c) of claim 1 comprises directly detecting said typable loci of said fragments that hybridize to said probes (column 18, lines 39-41 teach hybridization of the amplified products to an oligonucleotide microarray; column 20, lines 7-20 teach coupling a detectable label to the detection (i.e. address) probes).

Regarding claim 18, Dean teaches a method of detecting typable loci of a genome, comprising:

(a) amplifying genomic DNA with a population of random primers, thereby providing an amplified representative population of genome fragments comprising said typable loci (column 37, lines 10-39)

(b) contacting the amplified representative population of genome fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed (column 16, lines 26-50 teaches address probes less than 125 nucleotides in length; column 18, lines 39-41 teach hybridization of amplification products to these surface-immobilized probes)

(c) directly detecting typable loci of said probe-fragment hybrids (column 18, lines 39-41 teach hybridization of the amplified products to an oligonucleotide microarray; column 20, lines 7-20 teach coupling a detectable label to the detection (i.e. address) probes).

Regarding claim 19, Dean teaches that 9 copies of the native genome are amplified (column 39, lines 31-33).

Regarding claim 22, Dean teaches that the providing in step (a) comprises representationally amplifying a native genome (the amplification conducted in column 37, lines 10-39 is a representational amplification).

Regarding claim 25, Dean teaches disclose the method of claim 22, wherein said representationally amplifying comprises a single step reaction yielding a high complexity representation (column 37, lines 10-39 teach a single-step procedure).

Regarding claim 26, Dean teaches that at most 1×10^6 copies of the native genome are used as a template for amplification (column 39, lines 31-33, where 9 copies were used).

Regarding claim 28, Dean teaches that the substrate is a particle, a bead, a surface, a slide or a microchip (column 18, lines 23-38).

Regarding claim 29, Dean teaches that at least 100 typable loci are simultaneously detected (column 19, lines 51-52 teaches detection of 256 targets).

Regarding claim 30, Dean teaches the method of claim 18, wherein said genome is a human genome (column 37, lines 10-12).

Regarding claim 31, Dean teaches that step (b) of claim 18 comprises contacting the genome fragments with a multiplexed array of nucleic acid probes (column 18, lines 39-41).

Regarding claim 33, Dean teaches that the probes are nucleic acid probes that are at least 20 nucleotides in length (column 16, lines 26-50 teaches that the address probes described in column 18, lines 39-41 are less than 125 nucleotides in length, specifically 15-20 nucleotides in length).

Regarding claim 34, Dean teaches the method of claim 18, further comprising producing a report identifying said typable loci that are detected (column 17, lines 25-28).

Regarding claim 36, Dean teaches the method of claim 18, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to said probes (column 18, lines 39-41 teach hybridization of the amplified products to an oligonucleotide microarray; column 20, lines 7-20 teach coupling a detectable label to the detection (i.e. address) probes).

Regarding claims 78 and 79, Dean teaches that in the method of claims 1 and 18, the genomic DNA is amplified under isothermal conditions using a polymerase with strand displacement activity (see column 37, lines 36-37, where phi 29 DNA polymerase is used; see also column 24, lines 24-57).

Dean teaches that, "The most useful results from whole genome amplification are obtained when the amplification provides complete coverage of genomic sequences and minimal amplification bias (column 40, lines 51-54)." Dean further teaches that amplified and unamplified samples were analyzed by comparative genome hybridization and displayed indistinguishable hybridization patterns when signals from repetitive sequences were suppressed by CotI DNA (column 42, lines 4-16). However, Dean also teaches that in the absence of CotI suppression, some repetitive centromeric sequences were lost during the amplification (column

42, lines 16-19). Dean does not teach that the population of genome fragments generated by the amplification method comprises at least 90% of the genome as required by claims 1 and 18.

It would have been prima facie obvious to optimize the amplification reaction conditions taught by Dean to improve the level of genome coverage, since Dean taught that that, "The most useful results from whole genome amplification are obtained when the amplification provides complete coverage of genomic sequences and minimal amplification bias (column 40, lines 51-54)." An ordinary practitioner would have been motivated by this teaching of Dean to optimize the reaction conditions in order to maximize the level of genome coverage (e.g. to percentages greater than 90%), and thereby obtain more useful results from downstream analyses of the amplified products. As noted in MPEP 2144.05, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)." Routine optimization is not inventive, and no evidence has been presented to suggest that obtaining the claimed level of genomic coverage was conducted by a method other than routine optimization. Therefore, in the absence of secondary considerations, the methods of claims 1, 3, 6, 7, 9-12, 14, 15, 17-19, 22, 25, 26, 28-31, 33, 34, 36, 78, and 79 are prima facie obvious over Dean.

6. Claims 1, 3-7, 9-12, 14, 15, 17-19, 22-26, 28-31, 33, 34, 36, 78, and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schubert et al. (American Journal of Pathology (January 2002) 160(1): 73-79; cited previously) as evidenced by the following: Lindblad-Toh et al. (Nature Biotechnology (2000) 18: 1001-1005; cited previously), Zhang et al. (PNAS (1992) 89: 5847-5851; cited previously), and Roche technical information (cited previously) in view of Dean et al. (US 6,617,137 B2; cited previously) and further in view of Sun et al. (Nucleic Acids Research (1995) 23(15): 3034-3040; newly cited).

Regarding claim 1, Schubert teaches a method of detecting typable loci of a genome, comprising:

(a) amplifying genomic DNA with a population of random primers, thereby providing an amplified representative population of genome fragments comprising said typable loci, wherein the population comprises a high complexity representation (page 74, column 2 teaches whole genome amplification of genomic DNA by PEP according to the method taught by Zhang. Zhang teaches on page 5847 that PEP is conducted using random primers and generates a high complexity representation)

(b) contacting the amplified representative population of genome fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to the typable loci under conditions wherein probe-fragment hybrids are formed, wherein the probes are at most 125 nucleotides in length (page 75, column 1 teaches that gDNA subjected to PEP was hybridized to the HuSNP array as described by Lindblad-Toh. Lindblad-Toh teaches on page 1001 that the HuSNP array contains 25–mer probes for 1494 loci)

(c) detecting typable loci of the probe-fragment hybrids (page 77).

Regarding claim 3, Schubert teaches that the providing in step (a) comprises representationally amplifying a native genome (page 74, column 2, where PEP is a representational amplification method)

Regarding claim 4, Schubert teaches that the representationally amplifying comprises using a polymerase of low processivity (page 74, column 2 teaches that whole genome amplification was performed as taught by Zhang. Zhang teaches on page 5847, column 2, that Taq polymerase is used at 55°C). Under these conditions, Taq has low processivity (see Roche PCR applications manual, Chapter 2).

Regarding claim 5, the Taq polymerase used by Schubert inherently has a processivity rate of less than 100 bases per polymerization event (see Roche PCR applications manual, Chapter 2, where Taq polymerase is shown to have a processivity of 50 bp at the above reaction temperature).

Regarding claim 6, Schubert teaches that the representationally amplifying comprises a single step reaction yielding a high complexity representation (page 74, column 2 teaches that whole genome amplification was preformed as taught by Zhang. Zhang teaches on page 5847, that the PEP reaction comprises a single step reaction). A "single step reaction" has been interpreted to mean a "closed tube" reaction, because according to the specification, the term "a single step reaction" only appears to differentiate between the pooling of multiple, separate amplifications and performing a single amplification reaction (paragraph 153). Also, in the Examples, only single amplification reactions comprising multiple different temperature steps were conducted to produce representationally amplified samples. Therefore, the disclosure of Schubert as evidenced by Zhang meets the instant limitation.

Regarding claim 7, Schubert teaches that at most 1 x 10^6 copies of said native genome are used as a template for amplification (page 74, column 2, where the 7 ng of gDNA used by Schubert in the PEP reaction comprises approximately 350 copies of the native genome).

Regarding claim 9, Schubert teaches that the substrate is a surface (page 75, column 1, where the HuSNP array was used).

Regarding claim 10, Schubert teaches that at least 100 typable loci are simultaneously detected (see Figure 1 and Tables 3 and 4).

Regarding claim 11, Schubert teaches that the genome is a human genome (page 74).

Regarding claim 12, Schubert teaches that step (b) of claim 1 comprises contacting the genome fragments with a multiplexed array of nucleic acid probes (page 74, column 2 – page 75, column 1).

Regarding claim 14, Schubert teaches that the probes are nucleic acid probes that are at least 20 nucleotides in length (Schubert teaches hybridization of the genome fragments to the HuSNP array on page 75, column 1 as described by Lindblad-Toh. Lindblad-Toh teaches on page 1001 that this array consists of 25-mer probes for typing 1494 loci).

Regarding claim 15, Schubert teaches producing a report identifying said typable loci that are detected (the published is a report identifying the typable loci that were detected – see Figure 1 and Tables 3 & 4).

Regarding claim 17, Schubert teaches that step (c) of claim 1 comprises directly detecting said typable loci of said fragments that hybridize to said probes (page 75, column 1, where the HuSNP array is used to directly detect typable loci. See pages 1003-1004 of the cited reference Lindblad-Toh for further description of array hybridization and analysis).

Regarding claim 18, Schubert teaches a method of detecting typable loci of a genome, comprising:

(a) amplifying genomic DNA with a population of random primers, thereby providing an amplified representative population of genome fragments comprising said typable loci (page 74, column 2 teaches whole genome amplification of genomic DNA by PEP according to the method taught by Zhang. Zhang teaches on page 5847 that PEP is conducted using random primers)

(b) contacting the amplified representative population of genome fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed (page 75, column 1 teaches that gDNA subjected to PEP was hybridized to the HuSNP array as described by Lindblad-Toh. Lindblad-Toh teaches on page 1001 that the HuSNP array contains 25–mer probes for 1494 loci)

(c) directly detecting typable loci of said probe-fragment hybrids (page 77; See pages 1003-1004 of the cited reference Lindblad-Toh for further description of array hybridization and analysis).

Regarding claim 19, Schubert teaches that about 350 copies of the native genome are amplified (page 74, column 2, where the 7 ng of gDNA used by Schubert in the PEP reaction comprises approximately 350 copies of the native genome).

Regarding claim 22, Schubert teaches that the providing in step (a) comprises representationally amplifying a native genome (page 74, column 2, where the PEP whole genome amplification procedure is a representational amplification).

Regarding claim 23, Schubert teaches that the representatiorially amplifying comprises using a polymerase of low processivity (page 74, column 2 teaches that whole genome

amplification was performed as taught by Zhang. Zhang teaches on page 5847, column 2, that Taq polymerase is used at 55°C).

Regarding claim 24, Schubert teaches that the low processivity is less than 100 bases per polymerization event (see Roche PCR applications manual, Chapter 2, where Taq polymerase is shown to have a processivity of 50 bp at the above reaction temperature).

Regarding claim 25, Schubert teaches disclose the method of claim 22, wherein said representationally amplifying comprises a single step reaction yielding a high complexity representation (page 74, column 2 teaches that whole genome amplification was preformed as taught by Zhang. Zhang teaches on page 5847, that the PEP reaction comprises a single step reaction).

Regarding claim 26, Schubert teaches that at most 1 x 10^6 copies of the native genome are used as a template for amplification (page 74, column 2, where the 7 ng of gDNA used as a template correspond to approximately 350 copies of the native genome).

Regarding claim 28, Schubert teaches that the substrate is a surface (page 75, column 1, where the HuSNP array was used).

Regarding claim 29, Schubert teaches that at least 100 typable loci are simultaneously detected (see Figure 1 and Tables 3 and 4).

Regarding claim 30, Schubert teaches the method of claim 18, wherein said genome is a human genome (page 74).

Regarding claim 31, Schubert teaches that step (b) of claim 18 comprises contacting the genome fragments with a multiplexed array of nucleic acid probes (page 74, column 2 – page 75, column 1).

Regarding claim 33, Schubert teaches that the probes are nucleic acid probes that are at least 20 nucleotides in length (Schubert teaches hybridization of the genome fragments to the HuSNP array on page 75, column 1 as described by Lindblad-Toh. Lindblad-Toh teaches on page 1001 that this array consists of 25-mer probes for typing 1494 loci).

Regarding claim 34, Schubert teaches the method of claim 18, further comprising producing a report identifying said typable loci that are detected (the published is a report identifying the typable loci that were detected – see Figure 1 and Tables 3 & 4).

Regarding claim 36, Schubert teaches the method of claim 18, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to said probes (page 75, column 1, where the HuSNP array is used to directly detect typable loci. See pages 1003-1004 of the cited reference Lindblad-Toh for further description of array hybridization and analysis).

Schubert does not teach that the amplified representative population of genome fragments comprises sequences identical to at least 90% of the genome as required by independent claims 1 and 18. Schubert also does not teach that the genomic DNA is amplified under isothermal conditions using a polymerase having strand displacement activity as required by claims 78 and 79.

Dean teaches method of whole genome amplification based on strand displacement replication (see column 2, lines 40-54). Regarding claims 1 and 18, Dean teaches that, "The most useful results from whole genome amplification are obtained when the amplification provides complete coverage of genomic sequences and minimal amplification bias (column 40, lines 51-54)."

Regarding claims 78 and 79, the whole genome amplification method taught by Dean utilizes a polymerase with strand displacement activity and occurs under isothermal conditions (see column 37, lines 36-37, where phi 29 DNA polymerase is used; see also column 24, lines 24-57). Dean teaches that elimination of the denaturation step in the isothermal amplification method reduced sequence bias in the resulting amplified products (column 2, lines 54-61 and column 41, lines 20-46). Dean further teaches that use of the strand displacement polymerase results in the generation of a higher yield of amplified products in a shorter period of time compared to the PEP method taught by Schubert (column 3, lines 9-13 and column 4, lines 46-56).

Sun presents a mathematical analysis of the PEP method (page 3034, column 1). Sun teaches that under the PEP reaction conditions taught by Schubert and Zhang, approximately 78% of the genome is amplified (page 3034, column 1). Sun further teaches that a higher percentage of the genome may be amplified by using a high processivity polymerase (see page 3039, column 2).

It would have been prima facie obvious to optimize the PEP reaction conditions to improve the level of genome coverage, since Dean taught that that, "The most useful results from whole genome amplification are obtained when the amplification provides complete coverage of genomic sequences and minimal amplification bias (column 40, lines 51-54)." An ordinary practitioner would have been motivated by this teaching of Dean to optimize the reaction conditions in order to maximize the level of genome coverage (e.g. to percentages greater than 90%), and thereby obtain more useful results from downstream analyses of the amplified products. Since Sun taught that optimization of the reaction conditions by increasing primer

concentrations or substituting a high processivity polymerase could increase the level of genome coverage in PEP reactions (see page 3039, column 2), an ordinary practitioner of the method taught by Schubert would have been motivated by these teachings of Sun to optimize the PEP reaction conditions (e.g. by optimizing the primer concentration or substituting a different DNA polymerase) in order to improve the percentage of genomic coverage. Since Sun taught that greater than 90% coverage was theoretically possible (pages 3036 and pages 3038-3039), an ordinary practitioner would have had a reasonable expectation of success in optimizing the reaction conditions to obtain the claimed level of coverage. Finally, as noted in MPEP 2144.05, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)." Routine optimization is not inventive, and no evidence has been presented to suggest that obtaining the claimed level of genomic coverage was conducted by a method other than routine optimization. Therefore, in the absence of secondary considerations, the methods of claims 1, 3-7, 9-12, 14, 15, 17-19, 22-26, 28-31, 33, 34, and 36 are prima facie obvious over the cited references.

Regarding claims 78 and 79, it would also have been prima facie obvious for an ordinary practitioner of the method taught by Schubert to conduct the whole genome amplification reaction under isothermal conditions using a polymerase having strand displacement activity. As noted above, Dean taught that elimination of the denaturation step reduced sequence bias in the resulting amplified products (column 2, lines 54-61 and column 41, lines 20-46). Dean also taught that conducting whole genome amplification using polymerase with strand displacement activity resulted in an increased product yield in a shorter period of time (column 3, lines 9-13

and column 4, lines 46-56). An ordinary practitioner of the method taught by Schubert would have been motivated by these teachings of Dean to perform the whole genome amplification step under isothermal conditions using a polymerase with strand displacement activity in order to obtain these advantages of increased product yield and reduced sequence bias. Thus, the method of claims 78 and 79 is prima facie obvious in view of the combined teachings of Schubert, Dean, and Sun.

7. Claims 37-48, 50, 51, 53, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schubert et al. (American Journal of Pathology (January 2002) 160(1): 73-79; cited previously) as evidenced by the following: Lindblad-Toh et al. (Nature Biotechnology (2000) 18: 1001-1005; cited previously), Zhang et al. (PNAS (1992) 89: 5847-5851; cited previously), and Roche technical information (cited previously) in view of Pastinen et al. (Genome Research (1997) 7: 606-614; cited previously).

Regarding claim 37, Schubert teaches a method of detecting typable loci of a genome, comprising:

(a) amplifying genomic DNA with a population of random primers, thereby providing an amplified representative population of genome fragments comprising said typable loci, wherein the population of amplified genomic fragments comprises a high complexity representation (page 74, column 2 teaches whole genome amplification of genomic DNA by PEP according to the method taught by Zhang. Zhang teaches on page 5847 that PEP is conducted using random primers and generates a high complexity representation)

(b) contacting said genome fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to said typable loci under conditions wherein immobilized probe-fragment hybrids are formed (page 75, column 1 teaches that gDNA subjected to PEP was hybridized to the HuSNP array as described by Lindblad-Toh. Lindblad-Toh teaches on page 1001 that the HuSNP array contains 25–mer probes for 1494 loci)

(c) modifying said immobilized probe-fragment hybrids (page 75, column 1 teaches hybridization to the HuSNP array as described by Lindblad-Toh. Lindblad-Toh teaches on page 1004 that the probe-fragment hybrids were treated (or modified) by staining with streptavidin-phycoerythrin and biotinylated antistreptavidin antibody)

(d) detecting a probe or fragment modified in step (c), thereby detecting said typable loci of said genome (page 77; See pages 1003-1004 of the cited reference Lindblad-Toh for further description of array hybridization and analysis).

Regarding claim 38, the HuSNP array used by Schubert has probes for 1494 different targets (page 73, column 2 – page 74, column 1). These sequences are inherently linked to at least 10% of the expressed sequences of the human genome. Since the phrase "linked to" is very broad encompassing sequences that are linked genetically to one another as well as sequences that are derived from a particular nucleic acid sequence, the 1494 sequences taught by Schubert are inherently linked to at least 10% of the expressed sequences of the human genome.

Regarding claim 39, Schubert teaches that the providing in step (a) comprises representationally amplifying a native genome (page 74, column 2, where the PEP whole genome amplification procedure is a representational amplification).

Regarding claim 40, Schubert teaches that the representatiorially amplifying comprises using a polymerase of low processivity (page 74, column 2 teaches that whole genome amplification was performed as taught by Zhang. Zhang teaches on page 5847, column 2, that Taq polymerase is used at 55°C).

Regarding claim 41, Schubert teaches that the low processivity is less than 100 bases per polymerization event (see Roche PCR applications manual, Chapter 2, where Taq polymerase is shown to have a processivity of 50 bp at the above reaction temperature).

Regarding claim 42, Schubert teaches that said representationally amplifying comprises a single-step reaction yielding a high complexity representation (page 74, column 2 teaches that whole genome amplification was preformed as taught by Zhang. Zhang teaches on page 5847, that the PEP reaction comprises a single step reaction).

Regarding claim 43, Schubert teaches that at most 1 x 10^6 copies of said native genome are used as a template for amplification (page 74, where the 7 ng of gDNA used by Schubert in the PEP reaction corresponds to approximately 350 copies of the native genome).

Regarding claim 44, Schubert teaches that the nucleic acid probes are immobilized on a substrate (page 75, column 1, where the HuSNP array is an array of substrate-immobilized nucleic acid probes).

Regarding claim 45, Schubert teaches that the substrate is selected from the group consisting of a particle, bead, surface, slide, and microchip (page 75, column 1, where the HuSNP array is a surface comprising immobilized nucleic acid probes).

Regarding claim 46, Schubert teaches that least 100 typable loci are simultaneously detected (see Figure 1 and Tables 3 and 4).

Regarding claim 47, Schubert teaches disclose the method of claim 37, wherein said genome is a human genome (page 74).

Regarding claim 48, Schubert teaches the method of claim 37, wherein step (b) comprises contacting said genome fragments with a multiplexed array of nucleic acid probes (page 74, column 2 – page 75, column 1).

Regarding claim 50, Schubert teaches that the probes comprise nucleic acid probes that are at least 20 nucleotides in length (Schubert teaches hybridization of the genome fragments to the HuSNP array on page 75, column 1 as described by Lindblad-Toh. Lindblad-Toh teaches on page 1001 that this array consists of 25-mer probes for typing 1494 loci).

Regarding claim 51, Schubert teaches the method of claim 37, further comprising producing a report identifying said typable loci that are detected (the published is a report identifying the typable loci that were detected – see Figure 1 and Tables 3 & 4).

Schubert does not teach modifying the immobilized probe fragment hybrids by incorporation of one or more nucleotide analogs into the probes or fragments of the probe-fragment hybrids, as required by claim 37.

Pastinen teaches a method for detecting mutations in an oligonucleotide array-based format.

Regarding claim 37, the method of Pastinen comprises: (a) multiplex amplification of genomic DNA, (b) preparation of single-stranded templates, (c) hybridization of the single-stranded templates to an array of immobilized primers, (d) incorporating labeled nucleotide analog(s) into the immobilized primers, and (e) detecting the incorporated nucleotides (see Figure 1 and the Materials and Methods section on pages 611 and 613).

Regarding claims 53 and 54, the method taught by Pastinen is an single base extension assay (see page 607, column 2).

Further regarding claims 37, 53, and 54, Pastinen states, "Our results show that single-nucleotide primer extension is an excellent reaction principle for multiplex detection of mutations....When compared to hybridization using allele-specific oligonucleotide probes performed in the same array format, the power of discrimination between genotypes was at least one order of magnitude higher (page 607, column 2)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute solid-phase minisequencing as taught by Pastinen for the array hybridization taught by Schubert. An ordinary practitioner would have been motivated to do so, because Pastinen taught that single-nucleotide extension on an array of substrate-immobilized primers had a discrimination power at least one order of magnitude higher compared to hybridization using an array of immobilized allele-specific probes. Therefore, an ordinary practitioner would have been motivated to substitute solid-phase single-base extension for array hybridization in order to improve the discrimination power of the genotyping method. An ordinary practitioner would have had a reasonable expectation of success in substituting solid-phase single nucleotide extension for array hybridization, since both methods were designed to detect single nucleotide polymorphisms in genomic DNA. Thus, the method of claims 37-48, 50, 51, 53, and 54 is prima facie obvious in view of the combined teachings of Schubert and Pastinen.

8. Claims 37, 39-48, 50, 51, 53, 81, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schubert et al. (American Journal of Pathology (January 2002) 160(1): 73-79; cited previously) as evidenced by the following: Lindblad-Toh et al. (Nature Biotechnology (2000) 18: 1001-1005; cited previously), Zhang et al. (PNAS (1992) 89: 5847-5851; cited previously), and Roche technical information (cited previously) in view of Chee et al. (US 6,355,431 B1; cited on IDS) and further in view of Landegren et al. (Science (1988) 241: 1077-1080; newly cited).

Regarding claim 37, Schubert teaches a method of detecting typable loci of a genome, comprising:

(a) amplifying genomic DNA with a population of random primers, thereby providing an amplified representative population of genome fragments comprising said typable loci, wherein the population of amplified genomic fragments comprises a high complexity representation (page 74, column 2 teaches whole genome amplification of genomic DNA by PEP according to the method taught by Zhang. Zhang teaches on page 5847 that PEP is conducted using random primers and generates a high complexity representation)

(b) contacting said genome fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to said typable loci under conditions wherein immobilized probe-fragment hybrids are formed (page 75, column 1 teaches that gDNA subjected to PEP was hybridized to the HuSNP array as described by Lindblad-Toh. Lindblad-Toh teaches on page 1001 that the HuSNP array contains 25–mer probes for 1494 loci)

(c) modifying said immobilized probe-fragment hybrids (page 75, column 1 teaches hybridization to the HuSNP array as described by Lindblad-Toh. Lindblad-Toh teaches on page

1004 that the probe-fragment hybrids were treated (or modified) by staining with streptavidin-phycoerythrin and biotinylated antistreptavidin antibody)

(d) detecting a probe or fragment modified in step (c), thereby detecting said typable loci of said genome (page 77; See pages 1003-1004 of the cited reference Lindblad-Toh for further description of array hybridization and analysis).

Regarding claim 39, Schubert teaches that the providing in step (a) comprises representationally amplifying a native genome (page 74, column 2, where the PEP whole genome amplification procedure is a representational amplification).

Regarding claim 40, Schubert teaches that the representatiorially amplifying comprises using a polymerase of low processivity (page 74, column 2 teaches that whole genome amplification was performed as taught by Zhang. Zhang teaches on page 5847, column 2, that Taq polymerase is used at 55°C).

Regarding claim 41, Schubert teaches that the low processivity is less than 100 bases per polymerization event (see Roche PCR applications manual, Chapter 2, where Taq polymerase is shown to have a processivity of 50 bp at the above reaction temperature).

Regarding claim 42, Schubert teaches that said representationally amplifying comprises a single-step reaction yielding a high complexity representation (page 74, column 2 teaches that whole genome amplification was preformed as taught by Zhang. Zhang teaches on page 5847, that the PEP reaction comprises a single step reaction).

Regarding claim 43, Schubert teaches that at most 1×10^6 copies of said native genome are used as a template for amplification (page 74, where the 7 ng of gDNA used by Schubert in the PEP reaction corresponds to approximately 350 copies of the native genome).

Regarding claim 44, Schubert teaches that the nucleic acid probes are immobilized on a substrate (page 75, column 1, where the HuSNP array is an array of substrate-immobilized nucleic acid probes).

Regarding claim 45, Schubert teaches that the substrate is selected from the group consisting of a particle, bead, surface, slide, and microchip (page 75, column 1, where the HuSNP array is a surface comprising immobilized nucleic acid probes).

Regarding claim 46, Schubert teaches that least 100 typable loci are simultaneously detected (see Figure 1 and Tables 3 and 4).

Regarding claim 47, Schubert teaches disclose the method of claim 37, wherein said genome is a human genome (page 74).

Regarding claim 48, Schubert teaches the method of claim 37, wherein step (b) comprises contacting said genome fragments with a multiplexed array of nucleic acid probes (page 74, column 2 – page 75, column 1).

Regarding claim 50, Schubert teaches that the probes comprise nucleic acid probes that are at least 20 nucleotides in length (Schubert teaches hybridization of the genome fragments to the HuSNP array on page 75, column 1 as described by Lindblad-Toh. Lindblad-Toh teaches on page 1001 that this array consists of 25-mer probes for typing 1494 loci).

Regarding claim 51, Schubert teaches the method of claim 37, further comprising producing a report identifying said typable loci that are detected (the published is a report identifying the typable loci that were detected – see Figure 1 and Tables 3 & 4).

Schubert does not teach modifying the immobilized probe fragment hybrids by incorporation of one or more nucleotide analogs into the probes or fragments of the probe-fragment hybrids by extension-ligation.

Chee teaches methods of analyzing amplified products on arrays. Regarding claims 37, 53, 81, and 82, in Figure 7B Chee teaches hybridizing a target sequence 25 (which may be the product of an amplification reaction – see column 9, lines 14-25) to an immobilized oligonucleotide 45 to form a probe-target hybrid. The probe-target hybrid is then modified by ligation of an oligonucleotide probe 50 to the immobilized probe in the probe-target hybrid (see column 6, lines 60-65). This ligation reaction is an extension-ligation reaction, because the immobilized probe is extended via ligation. Chee also teaches that the probe can be extended with a polymerase prior to ligation (see column 18, lines 3-14).

Landegren teaches that detection of mutations, such as single nucleotide substitutions, using ligation-based detection is more specific than hybridization-based detection strategies because ligation depends on both proper hybridization and orientation of the probes (page 1078, column 1).

It would have been prima facie obvious to detect typable loci of the fragments amplified by the method of Schubert using the extension-ligation method taught by Chee, since Landegren taught that such ligation-based strategies were more specific than the hybridization detection method taught by Schubert (see page 1078, column 1). An ordinary practitioner would have been motivated to substitute ligation-based detection, as taught by Chee, for the hybridization-based detection taught by Schubert in order to obtain this improved specificity. Thus, the

combined teachings of Schubert, Chee, and Landegren result in the method of claims 37, 39-48, 50, 51, 53, 81, and 82.

9. Claims 13 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Schubert et al. (American Journal of Pathology (January 2002) 160(1): 73-79; cited previously) as evidenced by the following: Lindblad-Toh et al. (Nature Biotechnology (2000) 18: 1001-1005; cited previously), Zhang et al. (PNAS (1992) 89: 5847-5851; cited previously), and Roche technical information (cited previously) in view of Dean et al. (US 6,617,137 B2; cited previously) and further in view of Sun et al. (Nucleic Acids Research (1995) 23(15): 3034-3040; newly cited) and further in view of Maldonago-Rodriguez (Molecular Biotechnology, 1999; cited previously) **or** Dean et al. (US 6,617,137 B2) in view of Maldonago-Rodriguez (Molecular Biotechnology (1999) 11: 1-12; cited previously).

The combined teachings of Schubert, Dean, and Sun result in the method of claims 1 and 18, as discussed above. Also, the teachings of Dean render the method of claims 1 and 18 obvious.

These references do not teach contacting the array of nucleic acid probes with chaperone probes.

Maldonado-Rodriguez taught that preannealing auxiliary oligonucleotides to targets prior to contacting them with immobilized probes resulted in substantial increases in hybridization specificity and sensitivity as well as signal amplification (see abstract, especially points (1) – (4)). These auxiliary oligonucleotides are the functional equivalent of the instantly claimed chaperone probes.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize chaperone probes (or analogously "auxiliary oligonucleotides") as taught by Maldonado-Rodriguez in the method taught by either Schubert **or** Dean in order to improve hybridization specificity, sensitivity and amplify the observed signal. Maldonado-Rodriguez particularly pointed out that the preannealing of these chaperone probes to target sequences prior to hybridization to array-immobilized probes resulted in improved mismatch detection, amplification of the observed signal via base-stacking interactions between the chaperone probe and target sequence, and increased sensitivity by prevention of hybridization-blocking secondary structure formation in the target (see abstract and Discussion). These improvements to array-based hybridization experiments would have been directly applicable to the ordinary practitioner of the method taught by Schubert **or** Dean and would have strongly motivated this ordinary artisan to utilize chaperone probes as taught by Maldonado-Rodriguez in order to improve the hybridization-based analysis method in the ways outlined above.

10. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dean et al. (US 6,617,137 B2; cited previously) in view of Lipshutz et al. (Nature Genetics (1999) 21: 20-24; cited previously).

The teachings of Dean render the method of claim 18 obvious, as discussed above.

Dean teaches hybridization to high-density oligonucleotide arrays, but does not comment specifically as to how many different probes are present on the arrays.

Lipshutz teaches production and applications of high-density oligonucleotide arrays (see abstract). Regarding claims 21 and 38, Lipshutz teaches oligonucleotide arrays with 7,000 –

40,000 genes/ESTs per array (see Table 1 and Table 2), corresponding to greater than 10% of expressed human genes. Lipshutz teaches that these arrays are capable of quantitative and highly parallel expression monitoring (see abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a high-density oligonucleotide array as taught by Lipshutz to quantify amplification products generated by the method of Dean. Lipshutz expressly taught that the above high-density oligonucleotide arrays afforded the ability to simultaneously quantify more than 7,000 different genes (see Table 1). Since Dean taught that the multiple displacement amplification method described above was applicable to expression profiling (column 16, lines 51-67), an ordinary practitioner of this embodiment would have been motivated by the teachings of Lipshutz to monitor the expression profile using high-density oligonucleotide arrays, in order to obtain a rapid, quantitative, high-throughput method of monitoring the expression of a number of different genes. An ordinary practitioner would have expected a reasonable level of success in hybridizing the MDA products generated by the method of Dean to high-density oligonucleotide arrays, since Dean expressly taught hybridization to such arrays (column 18, lines 39-41). Therefore, one of ordinary skill in the art, interested in obtaining a rapid quantitative, high-throughput method of analyzing the amplified products generated by the method of Dean, would have been motivated to utilize the high-density oligonucleotide arrays taught by Lipshutz, thus resulting in the instantly claimed methods.

11. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over rejected under 35 U.S.C. 103(a) as being unpatentable over Schubert et al. (American Journal of Pathology

(January 2002) 160(1): 73-79; cited previously) as evidenced by the following: Lindblad-Toh et al. (Nature Biotechnology (2000) 18: 1001-1005; cited previously), Zhang et al. (PNAS (1992) 89: 5847-5851; cited previously), and Roche technical information (cited previously) in view of Pastinen et al. (Genome Research (1997) 7: 606-614; cited previously) and further in view of Maldonago-Rodriguez (Molecular Biotechnology (1999) 11: 1-12; cited previously).

The combined teachings of Schubert and Pastinen result in the method of claim 37, as discussed above.

These references do not teach contacting the array of nucleic acid probes with chaperone probes.

Maldonado-Rodriguez taught that preannealing auxiliary oligonucleotides to targets prior to contacting them with immobilized probes resulted in substantial increases in hybridization specificity and sensitivity as well as signal amplification (see abstract, especially points (1) – (4)). These auxiliary oligonucleotides are the functional equivalent of the instantly claimed chaperone probes.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize chaperone probes (or analogously "auxiliary oligonucleotides") as taught by Maldonado-Rodriguez in the method resulting from the combined teachings of Schubert and Pastinen in order to improve hybridization specificity, sensitivity and amplify the observed signal. Maldonado-Rodriguez particularly pointed out that the preannealing of these chaperone probes to target sequences prior to hybridization to array-immobilized probes resulted in improved mismatch detection, amplification of the observed signal via base-stacking interactions between the chaperone probe and target sequence, and increased sensitivity by prevention of

hybridization-blocking secondary structure formation in the target (see abstract and Discussion). These improvements to array-based hybridization experiments would have been directly applicable to the ordinary practitioner of the method resulting from the combined teachings of Schubert and Pastinen and would have strongly motivated this ordinary artisan to utilize chaperone probes as taught by Maldonado-Rodriguez in order to improve the hybridization-based analysis method in the ways outlined above.

12. Claims 64, 66, 67, 71, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schubert et al. (American Journal of Pathology (January 2002) 160(1): 73-79; cited previously) as evidenced by Zhang et al. (PNAS (1992) 89: 5847-5851; cited previously) in view of Pastinen et al. (Genome Research (2000) 10: 1031-1042; cited previously).

Schubert teaches a method for analyzing single nucleotide polymorphisms comprising whole genome amplification by primer extension preamplification (PEP) followed by microarray analysis using the HuSNP array (page 74, column 2 – page 75, column 1).

Regarding claim 64, Schubert teaches a method comprising:

(a) obtaining a high complexity representation of genomic DNA fragments by whole genome amplification using random primers (page 74, column 2)

(b) hybridizing the genomic DNA fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to typable loci, thereby forming a plurality of probe-fragment hybrids (page 74, column 2 – page 75, column 1)

(c) detecting typable loci of probe-fragment hybrids (page 75, column 1).

Regarding claim 67, Schubert teaches replication of the amplified genomic DNA fragments using a plurality of locus-specific primers (see page 74, column 2, where Schubert teaches that the PEP procedure was conducted as described in Zhang). Zhang teaches amplification of PEP fragments using locus-specific primers.

Schubert does not teach in vitro transcription of the population of amplified fragments to generate a population of RNA prior to array hybridization. Schubert also does not teach incorporation of nucleotide analogs into the probe-fragment hybrids.

Pastinen teaches a method for solid-phase genotyping on oligonucleotide microarrays.

Regarding claim 64, Pastinen teaches a method for detecting typable loci of a genome, comprising:

(a) in vitro transcribing a population of amplified genome fragments, thereby obtaining genomic RNA fragments (page 1038, "Multiplex PCR Amplification", where genomic DNA fragments are produced; page 1039 "Optimization of Allele-specific extension reactions" where in vitro transcription of the multiplex PCR products results in genomic RNA fragments; see also Figure 1 for a schematic)

(b) hybridizing said genomic RNA fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to said typable loci, thereby forming a plurality of immobilized RNA fragment-probe hybrids (page 1039 "Optimization of allele-specific extension reactions and Figure 1)

(c) detecting typable loci of said RNA fragment-probe hybrids (see Figure 1 and page 1039, column 1).

Regarding claim 66, Pastinen teaches that step (c) comprises modifying said genomic RNA fragment-probe hybrids with reverse transcriptase (page 1039 "Optimization of allele-specific extension reactions and Figure 1).

Regarding claim 71, Pastinen teaches that modifying the genomic RNA fragment-probe hybrids with reverse transcriptase occurs under conditions wherein DNA-dependent DNA synthesis is inhibited (Figure 1 and page 1039 where the absence of a DNA polymerase inhibits DNA-dependent DNA synthesis).

Regarding claim 72, Pastinen teaches that the method of claim 64 further comprises a step of isolating said genomic RNA fragments (Figure 1 and page 1039 where hybridization of the RNA fragments to specific array-immobilized targets results in their isolation).

Pastinen teaches that the solid-phase minisequencing method is more specific than allele-specific oligonucleotide hybridization for detection of mutations, such as single nucleotide polymorphisms (page 1038, column 1). Pastinen also teaches that RNA templates yielded higher signal-to-noise ratios than DNA targets (page 1033, column 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Pastinen to the genotyping method taught by Schubert. An ordinary practitioner would have been motivated to substitute solid phase minisequencing for hybridization, since Pastinen taught that the allele-specific extension step was more specific than hybridization with the allele-specific probes taught by Schubert (page 1038, column 1). An ordinary practitioner would also have been motivated to perform in vitro transcription and hybridize an RNA target to the immobilized primers, since Pastinen taught that RNA templates yielded higher signal-to-noise ratios than DNA (page 1033, column 1). An ordinary practitioner

would have recognized that application of these teachings of Pastinen would increase the sensitivity and specificity of the genotyping method. Therefore, the methods of claims 64, 66, 67, 71, and 72 are prima facie obvious over Schubert in view of Pastinen.

13. Claims 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schubert et al. (American Journal of Pathology (January 2002) 160(1): 73-79; cited previously) as evidenced by Zhang et al. (PNAS (1992) 89: 5847-5851; cited previously) in view of Pastinen et al. (Genome Research (2000) 10: 1031-1042; cited previously) and further in view of Grothues et al. (Nucleic Acids Research (1993) 21(5): 1321-1322; cited previously).

The combined teachings of Schubert and Pastinen result in the method of claim 66, as discussed above.

Neither Schubert nor Pastinen teach in vitro transcription using random primers comprising a 3' random sequence region and another region having a constant sequence.

Grothues teaches a method of amplification using tagged random primers (page 1321).

Regarding claims 68 and 69, Grothues teaches amplification using random primers containing a 3' random region and a 5' constant sequence to produce fragments labeled with a constant sequence (2nd paragraph, column 1, page 1321).

Regarding claim 70, Grothues teaches further amplification using a primer complementary to the constant tagged region (page 1321, column 1, 2nd paragraph).

Grothues teaches that the tagged primers can amplify virtually any nucleic acid sequence (page 1321, column 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Grothues to the method resulting from the combined teachings of Schubert and Pastinen. An ordinary practitioner would have been motivated to perform the in vitro transcription step using the tagged-primers, since Grothues taught that these primers could amplify virtually any nucleic acid sequence (page 1321, column 1). An ordinary practitioner would have recognized that the use of such primers would reduce artifacts in the results stemming from untranscribed sequences. Therefore, the methods of claims 68-70 are prima facie obvious in view of the combined teachings of Schubert, Pastinen, and Grothues.

14. Claim 80 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schubert et al. (American Journal of Pathology (January 2002) 160(1): 73-79; cited previously) as evidenced by the following: Lindblad-Toh et al. (Nature Biotechnology (2000) 18: 1001-1005; cited previously), Zhang et al. (PNAS (1992) 89: 5847-5851; cited previously), and Roche technical information (cited previously) in view of Pastinen et al. (Genome Research (1997) 7: 606-614; cited previously) and further in view of Dean et al. (US 6,617,137 B2; cited previously).

The combined teachings of Schubert and Pastinen result in the method of claim 37, as discussed above.

Neither Schubert nor Pastinen teach that the reaction is conducted under isothermal conditions using a polymerase having strand displacement activity.

Dean teaches method of whole genome amplification based on strand displacement replication (see column 2, lines 40-54). Regarding claim 80, the whole genome amplification method taught by Dean utilizes a polymerase with strand displacement activity and occurs under

isothermal conditions (see column 37, lines 36-37, where phi 29 DNA polymerase is used; see also column 24, lines 24-57). Dean teaches that elimination of the denaturation step in the isothermal amplification method reduced sequence bias in the resulting amplified products (column 2, lines 54-61 and column 41, lines 20-46). Dean further teaches that use of the strand displacement polymerase results in the generation of a higher yield of amplified products in a shorter period of time compared to the PEP method taught by Schubert (column 3, lines 9-13 and column 4, lines 46-56).

It would have been prima facie obvious for an ordinary practitioner of the method resulting from the combined teachings of Schubert and Pastinen to conduct the whole genome amplification reaction under isothermal conditions using a polymerase having strand displacement activity. As noted above, Dean taught that elimination of the denaturation step reduced sequence bias in the resulting amplified products (column 2, lines 54-61 and column 41, lines 20-46). Dean also taught that conducting whole genome amplification using polymerase with strand displacement activity resulted in an increased product yield in a shorter period of time (column 3, lines 9-13 and column 4, lines 46-56). An ordinary practitioner of the method resulting from the combined teachings of Schubert and Pastinen would have been motivated by these teachings of Dean to perform the whole genome amplification step under isothermal conditions using a polymerase with strand displacement activity in order to obtain these advantages of increased product yield and reduced sequence bias. Thus, the method of claim 80 is prima facie obvious in view of the combined teachings of Schubert, Pastinen, and Dean.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1, 3, 9, 12, 18, 22, 28, 31, 37, 39, 44, 45, 48, 53, and 54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 108, 119-121, 125-127, and 128-131 of copending Application No. 11/006,096. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 108, 119, 123, 125, 127, and 131 of the '096 application recite a more specific embodiment of the method more generically claimed in the instant claims 1, 18, and 37, and therefore, anticipate these claims. The limitations of the instant claims 3, 22, and 39 are recited in claim 108 of the '096 application. The limitations of the instant claims 9, 12, 28, 31, 44, 45, and 48 are recited in claims 119-121 of the '096 application. The limitations of the instant claims 53 and 54 are recited in claim 125 of the '096 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, 31, 37, 39, 40, 42, 44, 45, 48, 53, and 54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78-80, 82, 85, 86, 90, 92, 93, 98, 104-106, 108, 110, 111, 115, 117, 118, and 123 of copending Application No. 10/872,141 in view of Dean et al. (US 6,617,137 B2).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 78, 92, 104, and 117 of the '141 application recite a more specific embodiment of the method more generically claimed in the instant claims 1, 6, 18, and 25, with the exception that the claims of the '141 application do not teach that the amplification method generates fragments that cover at least 90% of the genome. Similarly, claims 78, 85, 92, 98, 104, 110, 117, and 123 of the '141 application recite a more specific embodiment of the method more generically claimed in the instant claims 37 and 42, with the exception that the claims of the '141 application do not teach that the amplification method generates fragments that cover at least 90% of the genome. Although the claims of the '141 application do not teach that the amplified products cover at least 90% of the genome, this limitation would have been obvious in view of the teachings of Dean. As discussed above, Dean teaches that whole genome amplification reactions are most useful when genome coverage is complete (column 40, lines 51-54). An ordinary practitioner would have been motivated by these teachings of Dean to optimize the reaction conditions of the method taught in the '141 application by routine experimentation in

order to achieve at least 90% coverage, and thereby, maximize the usefulness of the results obtained from downstream assays utilizing the amplified products. The limitations of the instant claims 3, 22, and 39 are recited in claims 90 and 115 of the '141 application. The limitations of the instant claims 4, 23, and 40 are recited in claims 93 and 118 of the '141 application. The limitations of the instant claims 9, 12, 28, 31, 45, and 48 are recited in claims 79, 80, 82, 105, 106, and 108 of the '141 application. The limitations of the instant claims 53 and 54 are recited in claim 86 and 111 of the '141 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, 31, 37, 39, 40, 42, 44, 45, 48, 53, and 54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78, 84, 86, 90, 91, 94, 95, and 100 of copending Application No. 10/871,513 in view of Dean et al. (US 6,617,137 B2).

Claims 78 and 94 of the '513 application recite the limitations of the instant claims 1, 6, 18, and 25, with the exception that the claims of the '513 application do not teach that the 90% of the genome is represented in the amplified products. Likewise, claims 78, 89, 90, 91, 94, and 100 of the '513 application recite the limitations of the instant claims 37 and 42, with the exception that the claims of the '513 application do not teach that the 90% of the genome is represented in the amplified products. Although the claims of the '513 application do not teach that the amplified products cover at least 90% of the genome, this limitation would have been obvious in view of the teachings of Dean. As discussed above, Dean teaches that whole genome

amplification reactions are most useful when genome coverage is complete (column 40, lines 51-54). An ordinary practitioner would have been motivated by these teachings of Dean to optimize the reaction conditions of the method taught in the '141 application by routine experimentation in order to achieve at least 90% coverage, and thereby, maximize the usefulness of the results obtained from downstream assays utilizing the amplified products. The limitations of the instant claims 3, 22, and 39 are recited in claim 78 of the '513 application. The limitations of the instant claims 4, 23, and 40 are recited in claim 95 of the '513 application. The limitations of the instant claims 9, 12, 28, 31, 45, and 48 are recited in claims 79, 84, and 86 of the '513 application. The limitations of the instant claims 53 and 54 are recited in claim 90 of the '513 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, 31, 37, 39, 40, 42, 44, 45, 48, 53, and 54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78, 81, 82, 84, 87, 91, 93, 94, and 104 of copending Application No. 10/871,710 in view of Dean et al. (US 6,617,137 B2).

Claims 78, 91, 93, and 104 of the '710 application recite the limitations of the instant claims 1, 6, 18, and 25, with the exception that the claims of the '710 application do not teach that the 90% of the genome is represented in the amplified products. Likewise, claims 78, 91, 93, 86-88, and 104 of the '710 application recite the limitations of the instant claims 37, and 42, with the exception that the claims of the '710 application do not teach that the 90% of the genome is represented in the amplified products. Although the claims of the '710 application do

not teach that the amplified products cover at least 90% of the genome, this limitation would have been obvious in view of the teachings of Dean. As discussed above, Dean teaches that whole genome amplification reactions are most useful when genome coverage is complete (column 40, lines 51-54). An ordinary practitioner would have been motivated by these teachings of Dean to optimize the reaction conditions of the method taught in the '141 application by routine experimentation in order to achieve at least 90% coverage, and thereby, maximize the usefulness of the results obtained from downstream assays utilizing the amplified products. The limitations of the instant claims 3, 22, and 39 are recited in claim 91 of the '710 application. The limitations of the instant claims 4, 23, and 40 are recited in claim 94 of the '710 application. The limitations of the instant claims 9, 12, 28, 31, 45, and 48 are recited in claims 79, 81, 82, and 84 of the '710 application. The limitations of the instant claims 53 and 54 are recited in claim 87 of the '710 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

20. Claim objections

Applicant's arguments, see pages 19 and 20, filed March 7, 2007, with respect to the objections to claims 9 and 36 have been fully considered and are persuasive. These objections have been withdrawn.

Rejections under 35 U.S.C. 102

Applicant's arguments, see pages 20-23, filed March 7, 2007, with respect to the rejection of claims 1, 3-7, 9-12, 14, 15, 17-19, 22-26, 28-31, 33, 34, 36, 37, 39-48, 50, and 51 under 102(b) as anticipated by Schubert and the rejection of claims 1-3, 6, 7, 9-12, 14, 15, 17-20, 22, 25, 26, 28-31, 33, 34, 36, 37, 39, 42-48, 50, 51, 64, 72, and 78-80 under 35 U.S.C. 102(e) as anticipated by Dean have been fully considered and are persuasive. Since neither reference teaches all of the elements of the amended claims, the rejections have been withdrawn.

Rejections under 35 U.S.C. 103

Applicant's arguments with respect to claims 13, 21, 32, 38, 49, 53, 54, 64, and 66-72 have been considered but are moot in view of the new ground(s) of rejection.

Double patenting rejections

Applicant's arguments with respect to the double-patenting rejections citing co-pending applications 11/006,096, 10/871,710, 10/872,141, and 10/871,153 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Art Unit 1637
May 23, 2007

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
5/25/07